



Surrogate Endpoints in Health Technology Assessment: An International Review of Methodological Guidelines

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Abstract

In the drive towards faster patient access to treatments, health technology assessment (HTA) agencies are increasingly faced with reliance on evidence from surrogate endpoints, leading to increased decision uncertainty. This study undertook an updated survey of methodological guidance for using surrogate endpoints across international HTA agencies. We reviewed HTA and economic evaluation methods guidance from European, Australian and Canadian HTA agencies. We considered how guidelines addressed the methods for handling surrogate endpoints, including (1) level of evidence, (2) methods of validation, and (3) thresholds of acceptability. Across the 73 HTA agencies surveyed, 29 (40%) had methodological guidelines that made specific reference to consideration of surrogate outcomes. Of the 45 methods documents analysed, the majority [27 (60%)] were non-technology specific, 15 (33%) focused on pharmaceuticals and three (7%) on medical devices. The principles of the European network for Health Technology Assessment (EUnetHTA) guidelines published in 2015 on the handling of surrogate endpoints appear to have been adopted by many European HTA agencies, i.e. preference for final patient-relevant outcomes and reliance on surrogate endpoints with biological plausibility and epidemiological evidence of the association between the surrogate and final endpoint. Only a small number of HTA agencies (UK National Institute for Care and Excellence; the German Institute for Medical Documentation and Information and Institute for Quality and Efficiency in Health Care; the Australian Pharmaceutical Benefits Advisory Committee; and the Canadian Agency for Drugs and Technologies in Health) have developed more detailed prescriptive criteria for the acceptance of surrogate endpoints, e.g. meta-analyses of randomised controlled trials showing strong association between the treatment effect on the surrogate and final outcomes. As the decision uncertainty associated with reliance on surrogate endpoints carries a risk to patients and society, there is a need for HTA agencies to develop more detailed methodological guidance for consistent selection and evaluation of health technologies that lack definitive final patient-relevant outcome evidence at the time of the assessment.

1 Background

A key issue in the increasing move towards early access to new and innovative healthcare technologies is the use of surrogate endpoints to support licensing and coverage decisions of such technologies. Within this context [1, 2], a surrogate endpoint is defined as a biomarker (e.g. blood pressure) or an intermediate outcome (e.g. exercise capacity) that can substitute for a final patient-relevant outcome that includes

mortality and health-related quality of life [3]. Disease areas with a strong tradition of surrogate endpoints include oncology (e.g. tumour response for overall survival) and cardiovascular disease (e.g. blood pressure for cardiovascular mortality or morbidity). In clinical areas (e.g. dermatology or acute disease) where patient-relevant outcomes are relatively quickly accrued, the need for surrogate endpoints is much less.

Many regulatory decisions across the world rely on surrogate endpoint evidence. Surrogate endpoints are the primary endpoints in almost half of the studies submitted to the US FDA for marketing approval of medicines [4, 5]. Recently, to inform the development pathways of medicines, the FDA published a list of accepted surrogate endpoints and disease areas that were the basis of approval or licensing of a

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Key Points for Decision Makers

Although surrogate endpoints enable faster trials and therefore faster access to treatment, they increase the uncertainty of coverage decisions on health technologies

Our survey shows that many international health technology assessment (HTA) agencies currently lack detailed guidance for the evaluation of health technologies that rely on surrogate endpoint evidence

HTA agencies need to provide more detailed and prescriptive guidelines for the consistent qualification and incorporation of surrogate endpoint evidence in the decision processes where the evidence on patient-relevant endpoints is lacking

Current best knowledge suggests that adequate approaches include evidence hierarchy frameworks, meta-regression analytical techniques and economic modelling methods that explicitly explore the uncertainty in the surrogate-to-final endpoint relationship

medicinal or a biological product under both the accelerated and the traditional approval pathways [6].

Whilst surrogate endpoints enable faster outcome accrual and therefore shorter clinical trials [7], reliance on such endpoints can be problematic if they fail to fully capture the complete risk–benefit profile of a health technology [8]. Surrogate endpoints have been shown to overestimate intervention effects [9] and, in some cases, lead to increased risk of harm [10, 11].

As the use of surrogate endpoints has become more common in the licensing of new health technologies [12], health technology assessment (HTA) agencies [12, 13] are under increasing pressure to utilise such evidence in their recommendations that inform the coverage and funding of medicines and medical devices. Whether surrogate endpoint evidence is used to interpret clinical effect in the context of insufficient final patient-relevant endpoint information [14] or is translated to a different outcome (such as quality-adjusted life-year [QALY]) within an economic model [15], there is a need to ensure that the choice of surrogate is adequate. Therefore, it has been recommended that the use of surrogate endpoints be limited only to those that have been validated appropriately [1, 12, 16]. Such validation ideally requires (1) experimental evidence that demonstrates (2) an acceptable association between treatment-induced change on surrogate endpoint and treatment-induced change on final patient-relevant endpoint and (3) a quantification of the treatment-induced change on final patient-relevant endpoint based on the observed treatment-induced change on surrogate endpoint [1].

In 2009, Velasco Garrido and Mangiapane [17] published a survey of methodological guidance across international HTA agencies. Although 20 of 34 methods guidelines were reported to include surrogate endpoints, the depth and breadth varied considerably between documents. The authors concluded that “the role of surrogate outcomes in HTA is very limited”, with many agencies accepting health technologies based on surrogate endpoint evidence in the absence of definitive final endpoint data as exceptional and only when the validity of the surrogate endpoint has been proven. However, few agencies provided details on how such ‘validity’ would actually be assessed.

Given recent developments in accelerated and adaptive licensing pathways, this study undertook an updated survey to gain a contemporary picture of methods for the handling of surrogate endpoints by international HTA agencies. As this study was conducted within the European Union-funded COMED (Pushing the boundaries of Cost and Outcome analysis of Medical Technologies) project [18], we also sought to assess whether these methods for handling surrogate endpoints included specific provision for medical device technologies.

2 Methods

We sought to identify recommendations on approaching surrogate endpoint evidence in HTA as reflected by current public guidelines and technical documents from relevant HTA bodies.

2.1 Identification of Health Technology Assessment (HTA) Agencies

We updated the listing of European HTA agencies from the previous 2009 survey of surrogate endpoints [17] to include all organizations currently listed as members of three major HTA networks (as of March 2018): Health Technology Assessment International, the European network for Health Technology Assessment (EUnetHTA) and the International Network of Agencies for Health Technology Assessment. We included all HTA agencies unless they were patient organisations, organisations whose members/stakeholders were the industry, and university centres, hospitals and professional organisations only involved in the production of HTA reports but not in policy guidance or methods development. Additionally, we included Australian and Canadian HTA agencies as they have been established for many years and therefore reflect ‘mature HTA settings’, i.e. the Australian Pharmaceutical Benefits Advisory Committee (PBAC), the Australian Medical Services Advisory Committee (MSAC) and the Canadian Agency for Drugs and Technologies in Health (CADTH). For each HTA agency, we checked

for the publicly available methodological guidance (in any language) either as guidelines or as methodological advisory documents (such as those of the UK National Institute for Health and Care Excellence [NICE] Decision Support Unit [19]). Agencies without available methods guidance were excluded.

2.2 Document Review and Data Extraction

We assessed the availability and the detail level of the guidance on the use of surrogate endpoints evidence in HTA processes that was provided by the included HTA organisations. Assessment included (1) terminology (including definitions) on the use of surrogate endpoints, (2) methods of surrogate validation and (3) methodological practices recommended in guidance documents.

2.3 Stage 1: Identification of HTA Agency Methods Guidance on the Use of Surrogate Endpoints

Websites of all included HTA agencies were screened using a combination of search terms (HTA, guidelines, methods, resources, publications, surrogate, intermediate and endpoints) to identify methods guidance availability and relevant methods documents. This was supplemented by hand searching of the relevant link categories on the websites. Where necessary, agencies were also contacted directly to enquire about relevant documents. For each included agency, the following data were extracted: (1) name of agency and country, (2) name and website location of the methods document, (3) language of the guideline, (4) text detailing use of surrogate endpoints (including location within the document and any citations referenced), (5) assessment of whether the guidance was specific to pharmaceuticals or medical devices or both and to certain disease areas (e.g. cancer). A data extraction form was developed and piloted by two authors (BG and OC) on a sample including documents in English, French and Italian to test the feasibility of the process and to ensure that captured data were appropriate and sufficient for the study's objective. The revised extraction form was then used by a single reviewer with language skills for each agency (OC, CF, BG, MM, SR, FD, KS, SdG, AZ) between April and July 2018. A random sample of 20 documents was then checked by a second reviewer (OC, BG, SR, SdG). For the purposes of presentation in this report, all text was translated into English.

2.4 Stage 2: Detailed Analysis of Surrogate Methodological Advice

For each agency identified in stage 1 as including advice on the use of surrogate endpoints in their methods guidance,

a more detailed data analysis framework was applied (see Table 1).

2.5 Data Analysis and Presentation

The findings of this survey are presented descriptively and in detailed summary results tables.

3 Results

3.1 Selection of HTA Agencies

A total of 73 HTA agencies met the inclusion criteria (see Fig. 1; Table 2); 29 were excluded because they had no published methodological guidance. Of the remaining 44 agencies, 29 (66%) included consideration of the handling of surrogate endpoints in their methods guidance. These 29 agencies included 18 European countries (Austria, Belgium, Bulgaria, Croatia, Germany, Spain, France, Germany, Hungary, Ireland, Italy, Netherlands, Norway, Poland, Portugal, Sweden, Slovakia, United Kingdom), the EUnetHTA network of agencies, and the agencies of PBAC, MSAC and CADTH. In total, 45 methodological guidance documents outlining the use of surrogate endpoints were included for analysis. Sources of these documents are presented in Table S1 in the electronic supplementary material (ESM).

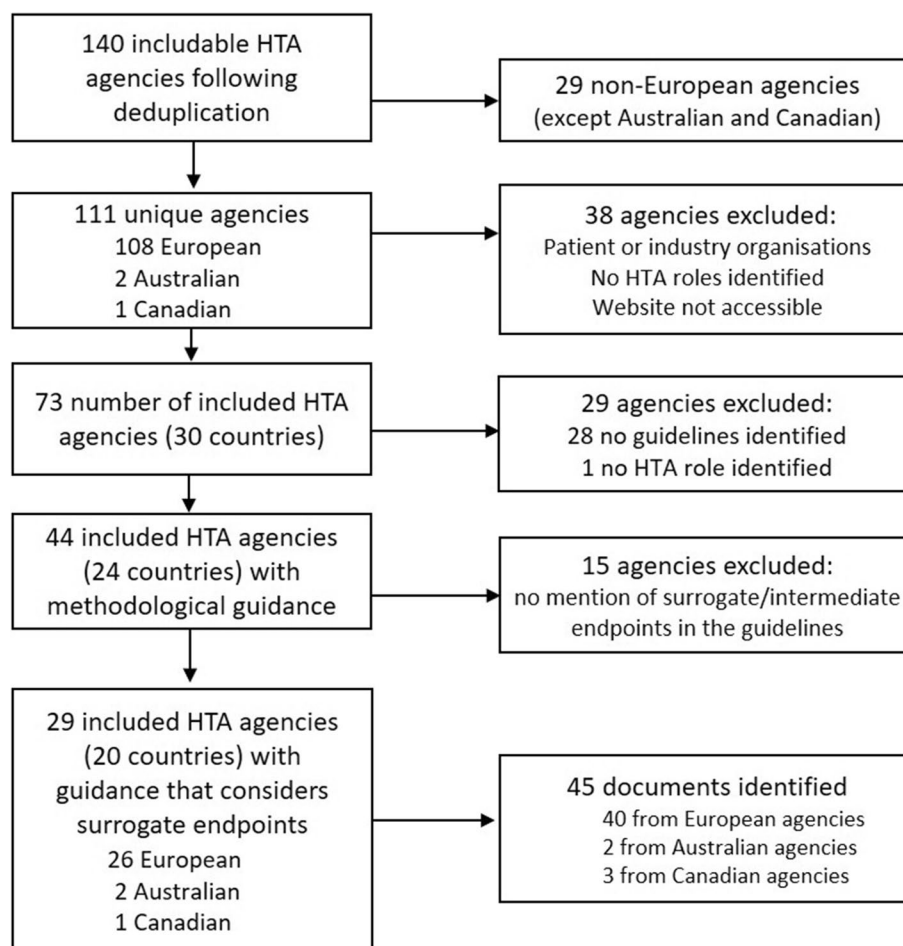
3.2 Consideration of Surrogate Endpoints

The extent to which methodological guidelines provided specific consideration on the use of surrogate endpoints varied greatly between agencies. The guidance documents of three (10%) HTA agencies (the Agency for Quality and Accreditation in Health Care and Social Welfare in Croatia (AAZ), the Galician Agency for Health Technology Assessment in Spain and the Norwegian Institute of Public Health) only mentioned surrogate endpoints in general terms and provided no specific methods guidance on their use.

Reflective of the collaborative partnership in the EUnetHTA project, methods guidance of many agencies was based on the guidance on surrogate endpoint methods published by the EUnetHTA in November 2015 [20]. Table 3 provides a summary of key aspects of the EUnetHTA guidance. Whilst the EUnetHTA guidelines state a preference for using final patient-relevant outcomes rather than surrogate outcomes, they also recognise the need to use surrogate/intermediate outcomes. For example, when evidence of the direct effect of the intervention on patient-relevant outcomes (such as mortality or health-related quality of life) is not available, the EUnetHTA guidelines propose criteria for acceptability of a surrogate endpoint: (1) a biological/

Table 1 Domains used to extract data from methods documents in stage 2

Domain	Explanation
Definition	Is a definition of surrogate endpoints provided as part of the document?
Examples	Are examples of surrogate endpoints provided in the text of the document (e.g. progression-free survival as a surrogate endpoint for overall survival)?
Use of surrogates considered	Are considerations on the use of surrogate endpoints included in the guidelines, such as recommendations to caution when including surrogate endpoints in the analysis?
Acceptability criteria	Are acceptability criteria included in the guidelines (e.g. requirements to validate the surrogate endpoint used)?
Evidence strength assessment	Is there a framework for quantifying the evidence on the surrogate–final outcome relationship? Level 1—evidence demonstrating that treatment effects on the surrogate correspond to effects on the patient-related outcome (from clinical trials); level 2—evidence demonstrating a consistent association between surrogate outcome and final patient-related outcome (from epidemiological/observational studies); level 3—evidence of the biological plausibility of the relationship between surrogate outcome and final patient-related outcome (from pathophysiological studies and/or understanding of the disease process)
Validation methods	Are any validation methods prescribed (e.g. correlation of the effects on the surrogate endpoint and the effects on the clinical endpoint from meta-analysis of randomised trials)?
Validation values	Are accepted cut-off values of the surrogate endpoint-to-final outcome association presented?

Fig. 1 Summary of agencies and documents selection. *HTA* health technology assessment

clinical plausibility for the endpoint, (2) evidence of an association with the final patient-relevant endpoint and (3) consideration of wider risk–benefit and/or public health implications [21].

3.2.1 Definition for Surrogate Endpoints

In total, 13 methods documents (29%) provided explicit definitions for surrogate endpoints, many of which were consistent with the EUnetHTA guideline definition, “biomarkers

Table 2 Included HTA agencies and summary of the availability of methodological guidance

Country	Acronym	Institution name		Language	Guidelines	Surrogate outcomes guidelines
		English	Original ^a			
Austria	HVB	Main Association of Austrian Social Security Institutions	Hauptverband der Österreichischen Sozialversicherungsträger	German	Yes	No
Austria	HVSV-HEK	Federation of the Austrian Social Insurance Institutions—Medicines Evaluation Commission	Hauptverband der österreichischen Sozialversicherungsträger—Heilmittel-Evaluierungskommission	German (mostly)	Yes	No
Austria	LBI-HTA	Ludwig Boltzmann Institute for Health Technology Assessment	Ludwig Boltzmann Institut für Health Technology Assessment	English	Yes	Yes
Austria	GÖG	Austrian Health Institute	Gesundheit Österreich GmbH	English	Yes	No
Australia	MSAC	Medical Services Advisory Committee		English	Yes	Yes
Australia	PBAC	Pharmaceutical Benefits Advisory Committee		English	Yes	Yes
Belgium	IPH ^b	Scientific Institute of Public Health	Sciensano	English	Yes	No
Belgium	KCE	Belgian Federal Health Care Knowledge Centre	Federaal Kenniscentrum voor de Gezondheidszorg	English	Yes	Yes
Belgium	RIZIV-INAMI	National Institute for Health Insurance	Rijksinstituut voor Ziekte- en Invaliditeitsverzekering	French	No ^c	No
Bulgaria	NCPHA	National Centre of Public Health Protection	Национален център по обществено здраве и анализи	Bulgarian	Yes	Yes
Canada	CADTH	Canadian Agency for Drugs and Technologies in Health		English	Yes	Yes
Central and Eastern Europe (Poland)	CEEStAHc	Central and Eastern European Society of Technology Assessment in Health Care		Polish	No	No
Croatia	AAZ	Agency for Quality and Accreditation in Health Care and Social Welfare	Agencija za kvalitetu i akreditaciju u zdravstvu i socijalnoj skrbi	Croatian	Yes	Yes
Croatia	CHIF	Croatian Health Insurance Fund	Hrvatski zavod za zdravstveno osiguranje	Croatian	No	No
Croatia	CIPH	Croatian Institute of Public Health	Hrvatski zavod za javno zdravstvo	Croatian	No	No
Cyprus	MoH CY	Ministry of Health of Cyprus	Υπουργείο Υγείας	Greek	No	No
Czech Republic	MoH CZ	Czech Republic Ministry of Health	Ministerstvo zdravotnictví ČR	English	No	No
Czech Republic	SUKL	State Institute for Drug Control	Státní ústav pro kontrolu léčiv	English (mostly)	Yes	No
Denmark	DEFACHTUM	DEFACHTUM	DEFACHTUM	English, Danish	Yes	No
EU	EUnetHTA	European Network for Health Technology Assessment		English	Yes	Yes
Finland	FIMEA	Finnish Medicines Agency	Lääkealan turvallisuus- ja kehittämiskeskus	English, Finnish	No	No
Finland	FinCCHTA	Finnish Coordinating Center for Health Technology Assessment	Kansallinen HTA-koordinaatioyksikkö	Finnish	Yes	No
Finland	FinOHTA	Finnish Office for Health Technology Assessment	Terveystieteiden tutkimuskeskus	English, Finnish	Yes	No
Finland	LH	Pharmaceuticals Pricing Board	Lääkkeiden hintalautakunta	English, Finnish	No	No

Table 2 (continued)

Country	Acronym	Institution name		Language	Guidelines	Surrogate outcomes guidelines
		English	Original ^a			
France	HAS	High Health Authority	Haute Autorité de Santé	French	Yes	Yes
Germany	DAHTA @ DIMDI	German Agency for HTA at the German Institute for Medical Documentation and Information	Deutsche Agentur für Health Technology Assessment	German	Yes	Yes
Germany	G-BA	The German Federal Health Care Joint Committee	Gemeinsame Bundesausschuss	German	Yes	Yes
Germany	IQWiG	Institute for Quality and Efficiency in Health Care	Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen	German	Yes	Yes
Germany	TAB	Office of Technology Assessment	Büro für Technikfolgen-Abschätzung beim Deutschen Bundestag (TAB)	English	No	No
Greece	EOF	National Organization for Medicines	Εθνικός Οργανισμός Φαρμάκων	Greek	No	No
Greece	EOPPY	National Organisation for Healthcare Provision	ΕΟΠΠΥ	Greek	Yes	Yes
Hungary	NIPN	National Institute of Pharmacy and Nutrition	Országos Gyógyszerészeti és Élelmezés-egészségügyi Intézet	Hungarian	Yes	Yes
Ireland	HIQA	Health Information and Quality Authority		English	Yes	Yes
Ireland	NCPE	National Centre for Pharmacoeconomics, St. James Hospital	National Centre for Pharmacoeconomics, St. James Hospital	English	No	No
Italy	Age.Na.S	National Agency for Regional Health Services	Agenzia nazionale per i servizi sanitari regionali	Italian	Yes	No
Italy	AIFA	Italian Medicine Agency	Agenzia Italiana Del Farmaco	Italian	Yes	Yes
Italy	Arsenal.IT	Veneto's Research Center for eHealth Innovation	Centro Veneto Ricerca e Innovazione per la Sanità Digitale	Italian	No	No
Italy	ASSR	Regional Observatory for Innovation—Regional Agency for Health and Social Care	Osservatorio regionale per l'innovazione—Agenzia sanitaria e sociale regionale—Regione Emilia-Romagna	Italian	No	No
Italy	DGFDm.IT	Italian Ministry of Health	Sede del Ministro—Ministero della salute	Italian	No	No
Italy	UVTA/AOP	HTA Unit in A. Gemelli Teaching Hospital	Unità di Valutazione delle Tecnologie (UVT), Policlinico Universitario "Agostino Gemelli"	Italian	Yes	Yes
Latvia	SAMLV	Zāļu valsts aģentūra	The State Agency of Medicines	Latvian (mostly)	No	No
Lithuania	HI LT	The Institute of Hygiene	Higienos institutas	English	No	No
Lithuania	VASPVT	State Health Care Accreditation Agency under the Ministry of Health of the Republic of Lithuania	Valstybinė akreditavimo sveikatos priežiūros veiklai tarnyba	English (some)	No	No
Malta	DPA/MoH	Directorate for Pharmaceutical Affairs		English	No	No
Norway	Hdir	Norwegian Directorate of Health	Helsedirektoratet	English (some)	No	No
Norway	NIPH	Formerly NOKC—The Norwegian Institute of Public Health	Nasjonalt kunnskapssenter for helse	English	Yes	Yes
Norway	NOMA	Norwegian Medicines Agency	Statens legemiddelverk	Norwegian	Yes	No

Table 2 (continued)

Country	Acronym	Institution name		Language	Guidelines	Surrogate outcomes guidelines
		English	Original ^a			
Poland	AOTMiT	Agency for Health Technology Assessment and Tariff System	Agencia Oceny Technologii Medycznych i Taryfikacji, Agency for Health Technology Assessment and Tariff System	Polish	Yes	Yes
Portugal	ACSS IP	Administração Central do Sistema de Saúde, I.P	Administração Central do Sistema de Saúde, I.P	English (mostly)	No	No
Portugal	INFARMED	National Authority of Medicines and Health Products	Autoridade Nacional do Medicamento e Produtos de Saúde	Portuguese	Yes	Yes
Romania	NSPHMPDB	National School of Public Health, Management and Professional Development	Scoala Nationala de Sanatate Publica, Management si Perfectionare in Domeniul Sanitar	English, Romanian	No	No
Slovakia	MoH SK	Ministry of Health of the Slovak Republic	Úrad verejného zdravotníctva Slovenskej republiky	Slovak (mostly)	Yes	Yes
Slovenia	JAZMP	Public Agency of the Republic of Slovenia for Medicinal Products and Medical Devices	Javna agencija Republike Slovenije za zdravila in medicinske pripomočke	Slovenian	No	No
Slovenia	NIJZ	National Institute of Public Health	Nacionalni inštitut za javno zdravje	English	No	No
Spain	AEETS	Spanish Association of Health Technology Evaluation	Asociación Española de Evaluación de Tecnologías Sanitarias	Spanish	Yes	Yes
Spain	AETSA	Andalusian Agency for Health Technology Assessment	Agencia de Evaluación de Tecnologías Sanitarias de Andalucía	Spanish	Yes	Yes
Spain	AQuAS	Agency for Health Quality and Assessment of Catalonia	Agència de Qualitat i Avaluació Sanitàries de Catalunya	Spanish	No	No
Spain	AVALLIA-T	Galician Agency for HTA	Avaliación de Tecnoloxías Sanitarias de Galician	Spanish	Yes	Yes
Spain	DGFPS MSPSI	Directorate General for Pharmacy and Health Care Products	Secretaría General de Sanidad y Consumo	Spanish	No	No
Spain	FPS	Andalusian Public Foundation Progress and Health	Fundación Pública Andaluza Progreso y Salud	Spanish	No	No
Spain	OSTEBA	Basque Office for Health Technology Assessment—Ministry for Health	Servicio de Evaluación de Tecnologías Sanitarias	English, Spanish	No	No
Spain	SESCS	Evaluation AND Planning Unit—Directorate of the Canary Islands Health Service	Servicio de Evaluación y Planificación, Canarias	Spanish	No	No
Sweden	SBU	Swedish Council on Technology Assessment in Health Care	Statens beredning för medicinsk utvärdering	English	Yes	Yes
Sweden	TLV	Dental and Pharmaceutical Benefits Agency	Tandvårds- och läkemedelsförmånsverket	English (some)	Yes	Yes
Switzerland	MTU-SFOPH	Medical Technology Unit—Swiss Federal Office of Public Health	Bundesamt für Gesundheit BAG	French, German	Yes	No
The Netherlands	ZIN	National Health Care Institute	Zorginstituut Nederland	English	Yes	Yes
The Netherlands	ZonMw ^d	The Netherlands Organisation for Health Research and Development		English	No	No
UK	AWMSG	All Wales Medicines Strategy Group		English	Yes	Yes

Table 2 (continued)

Country	Acronym	Institution name	Original ^a	Language	Guidelines	Surrogate outcomes guidelines
		English				
UK	AWTTC	All Wales Therapeutics and Toxicology Centre		English	No	No
UK	HIS	Healthcare Improvement Scotland		English	Yes	No
UK	HTW	Health Technology Wales	Technoleg Iechyd Cymru	English	Yes	No
UK	NICE	National Institute for Health and Clinical Excellence		English	Yes	Yes
UK	SMC	Scottish Medicines Consortium		English	Yes	No

HTA health technology assessment

^aBlank cells indicate the original name is also in English^bWIV-ISP merged with the veterinary agency to create Sciensano in April 2018^cOnly administrative procedure described^dExcluded at a later stage, no HTA role

and intermediate endpoints” that can “substitute for a clinically meaningful (final) endpoint”. Guidelines from PBAC [22], MSAC [23] and CADTH [24] use similar definitions. For instance, surrogate outcomes are considered by CADTH as “a subset of intermediate outcomes” and are defined as “a laboratory measurement or a physical sign used as a substitute for a clinically meaningful end point that measures directly how a patient feels, functions, or survives” [24]. In their glossary of terms, PBAC defines surrogate outcomes as “a variable that is suspected, but not necessarily demonstrated, to occur on the causal pathway from a clinical management or factor to the clinically relevant final outcome” and recommend the justification and validation of any surrogate outcome used in the analysis [22].

3.2.2 Example of Surrogate Endpoints

In total, 18 documents (40%) provided specific examples of surrogate endpoints (e.g. “Blood pressure as a surrogate endpoint for cardiovascular mortality; bone mineral density as a surrogate for bone fracture; HIV1-RNA viral load as an indicator of viral suppression”, Health Information and Quality Authority, Ireland). A support document from the German Institute for Medical Documentation and Information (DIMDI) [25] also provides examples where surrogate endpoints have been proven not to be good surrogates (e.g. increased bone density following treatment of osteoporosis with sodium fluoride did not result in an observed decrease in fractures). A total of 44 documents (98%) included some consideration of the use of surrogates in the analysis (e.g. “only use a surrogate outcome if it has a well-established link (i.e., validated) with one of (final) outcomes”, CADTH). While some guidelines seemed to implicitly consider the surrogate endpoints in a cost-effectiveness context (NICE, PBAC, CADTH), most did not seem to differentiate the interpretation of surrogate endpoints according to the domain (e.g. clinical efficacy, cost effectiveness, etc.). Only four guidelines (from the Austrian Ludwig Boltzmann Institute for Health Technology Assessment, the AAZ, the Polish Agency for Health Technology Assessment and Tariff System (AOTMiT) and CADTH) mentioned the use of surrogate outcomes for safety.

3.2.3 Acceptability of Surrogate Endpoints

In total, 26 guidelines (52%) provided discussion on the acceptability of surrogate endpoints [e.g. “If there is data that validates a surrogate, then these will be assessed in terms of their relevancy and their credibility”, German Institute for Quality and Efficiency in Health Care (IQWiG)]. Nine (18%) clearly refer to the association between surrogate endpoint and final outcome.

Table 3 Overview of EUnetHTA guidelines for surrogate endpoints

Use of surrogates considered?	Yes (dedicated document) Surrogate endpoints “should be adequately validated: the surrogate–final endpoint relationship must have been demonstrated based on biological plausibility and empirical evidence.”
Surrogate definition provided?	Yes “A surrogate endpoint is an endpoint that is intended to replace a clinical endpoint of interest that cannot be observed in a trial—it is a variable that provides an indirect measurement of effect in situations where direct measurement of clinical effect is not feasible or practical. (ICH guideline E9, Statistical Principles for Clinical Trials, 1998) A surrogate endpoint may be a biomarker that is intended to substitute for a clinical endpoint. A surrogate endpoint may also be a clinical endpoint that is used to replace the endpoint of interest, such as an intermediate clinical endpoint.” “A biomarker can be defined as a characteristic that is objectively (reliably and accurately) measured and evaluated as an indicator of normal biological processes, pathogenic processes, or pharmacologic responses to an intervention” (Biomarkers Definitions Working Group, 2001) “An intermediate endpoint is a clinical endpoint such as measure of a function or of a symptom (disease-free survival, angina frequency, exercise tolerance) but is not the ultimate endpoint of the disease, such as survival or the rate of irreversible morbid events (stroke, myocardial infarction)” (Temple et al. 1999)
Examples of surrogates listed?	Yes Example of surrogate endpoints: biomarkers (e.g. cholesterol level, HbA1c); examples of intermediate endpoints: disease-free survival, angina frequency, exercise tolerance
Acceptability criteria provided?	Yes “Before a biomarker can be accepted as a surrogate endpoint, there is a need to have confidence that changes in the biomarker reliably predict changes in the desired clinical endpoints” (EMA, 2007)
Evidence strength assessment provided?	Yes “The evidence for the validation of the surrogate–final outcome relationship has been presented by taking into account the level of evidence: Level 1: evidence demonstrating that treatment effects on the surrogate endpoint correspond to effects on the patient-related clinical outcome (from clinical trials); comprises a meta-analysis of several RCTs and establishment of correlation between effects on the surrogate and clinical endpoint Level 2: evidence demonstrating a consistent association between surrogate endpoint and final patient-related endpoint (from epidemiological/observational studies); and Level 3: only evidence of biological plausibility of relationship between surrogate endpoint and final patient-related endpoint (from pathophysiological studies and/or understanding of the disease process)”
Validation methods provided?	Yes While the guidelines state that “currently, there is no systematic, transparent and widely agreed-upon process of biomarker validation”, they quote correlation of the effects on the surrogate and the effects on the clinical endpoint based on meta-analyses of several RCTs, as well as the surrogate threshold effect [39] The document offers a selected bibliography addressing the statistical methods of surrogate validation
Validation values provided?	Yes Although only for information purposes: “There is no clear consensus of which correlation values are sufficient to assume adequate surrogacy, but values of between about 0.85 and 0.95 are often discussed”

HbA1c glycated haemoglobin, *ICH* International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use, *RCT* randomised controlled trial

3.3 Detailed Methodological Guidance on Surrogate Endpoints

In addition to the EUnetHTA guidelines, seven (15%) HTA agencies had methods guidance that included detailed methodological consideration of surrogate endpoints: IQWiG (two documents), NICE, AOTMiT, the Portuguese National Authority of Medicines and Health Products (INFARMED), PBAC, MSAC and CADTH. These documents included recommendations of methods to be used for the validation

of surrogate endpoints and, in two cases, cut-offs for the acceptance of surrogates according to their validation.

3.3.1 Methods for Validation of Surrogate Endpoints

Specific methods recommendations are listed in Table 4. EUnetHTA [20] and IQWiG [26] guidelines are the most detailed and prescriptive European guidelines, providing suggestions of methods for the validation of surrogate outcomes and defining necessary correlation levels for

the association between surrogate and clinically relevant outcomes [27]. In contrast, NICE technology appraisal guidelines [28] focus on the decision uncertainty associated with evidence and this reflected in the economic modelling of a technology and recommend that “in all cases, the uncertainty associated with the relationship between the end point and health-related quality of life or survival should be explored and quantified” [29]. PBAC guidance [22] contains a supplementary appendix that outlines a prescriptive approach to validating surrogate endpoints for decision modelling based on a four-step approach: (1) identify the surrogate endpoints and the corresponding final outcome; (2) establish the biological plausibility of the two, and present epidemiological evidence to support it; (3) present randomised trial evidence to support the nature of the relationship; (4) translate the treatment effect on the surrogate endpoints to an estimate of the comparative treatment effect for the final outcome [22].

3.3.2 Specific Guidance for Disease Areas

In three cases, specific guidance on the use of surrogate endpoints in oncology was available: NICE [30] analysed the suitability of particular surrogate endpoints (such as progression-free survival for overall survival in cancer), and IQWiG [27] provided a detailed discussion on the potential use of surrogate outcomes in oncology. In CADTH guidance, a document dedicated to the evaluation of oncology therapies [31] contained detailed discussion of acceptability of surrogate outcomes according to their correlation with patient outcomes and the treatment intent (curative, adjuvant or palliative).

3.3.3 Specific Guidance for Medical Devices

Of the 45 methods documents analysed, 15 (33%) were exclusively intended for pharmaceuticals, and only three (7%) were intended exclusively for the evaluation of medical devices (NICE Medical Technology Evaluation Programme (MTEP), the State Institute for Drug Control in the Czech Republic and MSAC). Table 5 provides a comparison of the methods guidelines across HTA programmes aimed at evaluating either general health technologies or pharmaceuticals versus those for evaluating medical devices in the UK (NICE technology appraisal vs. MTEP) and Australia (PBAC vs. MSAC). Guidelines for medical devices appeared less specific and did not include any specific methodological recommendations beyond a general need to provide supporting evidence for surrogate endpoints (Table 5).

4 Discussion

Our updated international survey included 74 HTA agencies, of which 29 (39%) had methodological guidance documents that included consideration of surrogate endpoints. Many of the European agencies' methods guidelines appear to have been revised to reflect the principles of the EUnetHTA guidelines on surrogate endpoints published in 2015 [20]. The EUnetHTA guidelines state a preference for evidence from final patient-relevant outcomes (such as mortality and health-related quality of life) and advise cautious consideration when surrogate endpoints are used, i.e. use of ‘validated’ surrogate endpoints. However, although the EUnetHTA guidelines are a useful development, they do not provide any explicit criteria to establish whether or not a surrogate endpoint is valid. Furthermore, none of the HTA guidelines in our survey included a list of ‘accepted’ surrogate endpoints, i.e. surrogate endpoints for which the future use in an evaluation would not require justification.

We identified only five HTA agencies (IQWiG, DIMDI, NICE, PBAC and CADTH) with guidelines providing specific prescriptive methodological advice on the statistical methods that should be used for the validation and assessment of acceptability of surrogate endpoints. Whilst there was a recognition across these guidelines of the lack of methodological consensus around the level of evidence necessary for the validation of surrogates, consensus was strong on the need for randomised trial data to support the association in the treatment effect between surrogate and final endpoints, including the use of meta-regression analysis methods. However, only a IQWiG document currently discusses numerical values for an acceptable level of association (e.g. R^2 trial > 0.49) [27]. Our results showed little difference in guidance between the use of surrogate endpoints for clinical effectiveness and for incorporation into economic models, with the exception of the NICE technical guidance approach, which focuses on the exploration of uncertainty in the surrogate-to-final-outcome relationship as part of the probabilistic sensitivity analysis. Since our study was conducted, the NICE decision support unit published another technical document [32]. This report focused on the use of multivariate meta-analytic methods for combining data from multiple correlated outcomes for the purpose of surrogate endpoint evaluation and suggested that, instead of criteria about the correlation, it is important to look at predicted estimates and their uncertainty because the strength (or weakness) of the surrogate relationship will manifest itself in the width of the predicted interval of the treatment effect on the final outcome.

The majority of methodological documents on surrogate endpoints identified in our study were intended to be applied

Table 4 HTA agencies with detailed methods for the handling of surrogate endpoints

Agency	Methods for validation of surrogate endpoints	Cut-offs for the acceptance of surrogate endpoints
MSAC (Australia)	<p>MSAC propose a three-step approach to validate the transformation of a surrogate endpoint to estimate final outcomes:</p> <p>Step 1 requires a systematic review “to examine whether epidemiological evidence and biological reasoning has established that there is a relationship between the surrogate outcome and the final outcome independent of any intervention”</p> <p>Step 2 requires a systematic review “to examine whether direct randomised trial evidence using other active medical services has shown that there is a basis to conclude that a treatment effect on the surrogate outcome has satisfactorily predicted a treatment effect on the final outcome. [...] Based on this evidence, quantify the relationship between these treatment effects with an assessment of the uncertainty of the relationship”</p> <p>Step 3 requires an explanation “why this relationship between the treatment effects on these outcomes with these other active medical services is likely to apply to the proposed therapeutic medical service. [...] At present, it is difficult to give categorical advice” [23]</p>	Not reported
PBAC (Australia)	<p>PBAC propose a four-step approach to validating the use of a surrogate endpoint to predict a final outcome:</p> <p>A5.1—Define the PSM and the TCO</p> <p>A5.2—Establish the biological reasoning for the link between the PSM and the TCO, including how pivotal the PSM is to the causation pathway of the TCO, and present epidemiological evidence to support this</p> <p>A5.3—Present randomised trial evidence to support the nature of the PSM–TCO comparative treatment effect relationship</p> <p>A5.4—Translate the comparative treatment effect on the PSM from the studies included in Part A, Subsection 2.2, to an estimate of the comparative treatment effect for the TCO.” [22]</p>	Not reported
CADTH (Canada)	<p>“Validated surrogate outcomes are proven to be predictive of an important patient outcome. A surrogate outcome is valid only if there is a “strong, independent, consistent association” with an important patient outcome, and there is “evidence from randomized trials that ... improvement in the surrogate end point has consistently lead to improvement in the target outcome.” [24]</p>	Not reported
DIMDI (Germany)	<p>No gold standard for the validation of surrogate endpoints, but approaches based on several studies, such as meta-analyses, are preferred</p> <p>Regardless of statistical method used for validation, validation should be considered as technology specific [25]</p>	Not reported
G-BA (Germany)	<p>Correlation from meta-analyses between effects on the surrogate outcome and the final outcome [39, 40]</p> <p>Surrogate Threshold Effect [41]</p>	Not reported
IQWiG (Germany)	<p>No ‘best’ method is defined, but correlation-based validation is the ‘preferred’ method, in the sense it has been most widely used in evaluations. Another option discussed is the surrogate threshold effect [26]</p> <p>A support document [27] discusses threshold values reported in the literature, without enforcing them</p>	<p>“A correlation of $R \geq 0.85$; $R^2 \geq 0.72$ measured at the lower bound of the 95% percentage interval allows to conclude that the validation study represents a high reliable result. This interval $R < 0.85$; $R^2 < 0.72$ to $R > 0.7$; $R^2 > 0.49$ represents a medium reliable result between surrogate and patient-relevant endpoint. If a validation study shows high reliable results with statistically low correlation ($R \leq 0.7$; $R^2 \leq 0.49$) measured at the lower bound of the confidence interval then the surrogate is not considered as a valid endpoint” [27]</p>

Table 4 (continued)

Agency	Methods for validation of surrogate endpoints	Cut-offs for the acceptance of surrogate endpoints
EUnetHTA	Correlation from meta-analyses of several RCTs between the effects on the surrogate and the effects on the clinical endpoint If there is no high correlation demonstrated, conclusions might still be made if the surrogate threshold effect is considered [41]	“Values of between about 0.85 and 0.95 are often discussed”
AOTMiT (Poland)	“If the clinical effectiveness assessment is based on the results of surrogate endpoints, the clinical analysis must reliably demonstrate their relationship with the clinically significant outcomes. Validation of the surrogate endpoints should be carried out in relation to the health problem in question.” Cites EUnetHTA guidelines for methods	Not reported
INFARMED (Portugal)	Seems to use the framework proposed by Bucher et al. [14] “For a surrogate measure to be validated, the following questions should be positively answered: 1. Does a strong, consistent and independent association exist between the surrogate outcome and the clinically relevant outcome? This criterion is necessary but not sufficient in itself; 2. Are there any randomized studies on the same class of medicines, where improvements in the surrogate outcomes corresponded to improvements in clinically relevant outcomes? 3. Are there any randomized studies on different classes of medicines, where improvements in the surrogate outcomes corresponded to improvements in clinically relevant outcomes for the patient?”	To be considered as validated, a surrogate outcome must comply with criteria from 1 to 3. Verification of these criteria usually requires a meta-analysis of randomized studies
NICE (UK)	Guidelines are not specific on the validation methods but emphasise that “in all cases, the uncertainty associated with the relationship between the end point and health-related quality of life or survival should be explored and quantified”	Not reported

CADTH Canadian Agency for Drugs and Technologies in Health, *DIMDI* Institute for Medical Documentation and Information, *EUnetHTA* European network for Health Technology Assessment, *G-BA* The German Federal Health Care Joint Committee, *IQWiG* Institute for Quality and Efficiency in Health Care, *MSAC* Medical Services Advisory Committee, *NICE* National Institute for Care and Excellence, *PBAC* Pharmaceutical Benefits and Advisory Committee, *PSM* proposed surrogate measure, *RCT* randomised controlled trial, *TCO* target clinical outcome

across health technologies (medicine, medical device or others) and across medical conditions. Given that the development and use of surrogate endpoints has become particularly common in oncology [33, 34], NICE, IQWiG and CADTH have published specific support documents for the use of surrogates in this clinical area [27, 30, 31]. Commonly used surrogate endpoints for the final outcome of overall survival in cancer include progression-free survival, disease-free survival and tumour response.

Pharmaceuticals and medical devices traditionally have different regulatory and evidence-generation pathways [35]. Given that various countries/agencies have separate HTA processes for the evaluation of medicines and medical devices, we could compare their methodological approaches to the consideration of surrogate endpoints [36]. The NICE technology appraisal is applicable to all medical technologies, whereas the NICE MTEP specifically considers

medical devices and diagnostics. Similarly, in Australia, PBAC assesses pharmaceuticals and MSAC assesses medical devices. The PBAC and MSAC guidance on surrogate endpoints was similar, but we found more of a difference within NICE programmes. The NICE technology appraisal programme was much more detailed and directive in guidance than the MTEP, reflecting the traditionally greater evidence requirements for medicines than for devices. Whilst it might be expected that the evidence requirements for the use and validation of surrogate endpoints should not necessarily differ between health technologies and across disease areas, we recognise there may be challenges in application. For example, given the current regulatory requirements, for specific medical devices, randomised controlled trial (RCT) (and sometimes, non-RCT)-level evidence may not be available at the time of HTA appraisal and even after it [35, 37]. It is likely that the requirement of ‘several RCTs’ for good

Table 5 Surrogate endpoint guidance in medical device-specific HTA programmes compared with pharmaceuticals programmes

	NICE TA guidance ^a		NICE MTEP guidance ^b		PBAC	MSAC
Type of technologies	Pharmaceuticals		Medical devices		Pharmaceuticals	Medical devices
Use of surrogates considered?	Yes		Yes—although guidance refers broadly to “intermediate outcomes” rather than surrogate endpoints, the guidance acknowledges the limited nature of evidence usually available for medical devices		Yes	Yes
Surrogate definition provided?	Yes—“intermediate outcome—outcomes that are related to the outcome of interest but may be more easily assessed within a clinical study”		No		Yes—outcomes of RCTs “that are of less patient relevance than intended final outcomes of treatment”	Yes—“a variable that occurs in a causal pathway from a clinical management or factor to the final outcome”
Examples of surrogates listed?	Yes—“for example, blood pressure reduction is related to the risk of a stroke”		No		Yes—e.g. “viral load and cure of viral hepatitis”	Yes—e.g. “cholesterol for cardiovascular events”
Acceptability criteria provided?	No—guidance does not provide explicit criteria		No		Yes—“to transform a surrogate outcome to predict a treatment effect on the intended final outcome, explain and justify the method of this transformation, including a justification for how the relationship might vary over time”	Yes—“present a surrogate outcome (that is not the primary outcome) only when it is critical to the therapeutic conclusion or economic evaluation”
Evidence strength assessment provided?	Yes—while not providing a structured framework, guidance stipulates that “evidence in support of the surrogate-to-final end point outcome relationship must be provided together with an explanation of how the relationship is quantified for use in modelling. The usefulness of the surrogate end point for estimating QALYs will be greatest when there is strong evidence that it predicts health-related quality of life and/or survival. In all cases, the uncertainty associated with the relationship between the end point and health-related quality of life or survival should be explored and quantified”		No		Yes—a three-step framework is proposed: Step 1: provide epidemiological evidence and biological reasoning on the relationship between the surrogate outcome and the final outcome “independent of any intervention” Step 2: provide evidence where similar interventions’ effect on the surrogate outcome predicts an effect on the final outcome Step 3: explain why evidence from previous steps is likely to apply to the proposed technology	Yes—a four-step approach to integrating SE is proposed: “A5.1—Define the [SE] and the [final outcome] A5.2—Establish the biological reasoning for the link between the [SE] and the [final outcome] [...] and present epidemiological evidence to support this A5.3—Present randomised trial evidence to support the nature of the [surrogate-final outcome] relationship A5.4—Translate the comparative treatment effect on the [SE] to an estimate of the [...] treatment effect for the [final outcome]”

Table 5 (continued)

	NICE TA guidance ^a	NICE MTEP guidance ^b	PBAC	MSAC
Validation methods provided?	No	No	Yes—"investigations of heterogeneity, treatment effect variation, subgroup analysis and/or meta-regression"	Yes—multi-trial meta-regression, single trial or small number of randomised trials where individual patient data are available, one randomised trial, no randomised trial data
Validation cut-off values provided?	No	No	No	No

HTA health technology assessment, MSAC Medical Services Advisory Committee, MTEP Medical Technologies Evaluation Programme, NICE National Institute for Care and Excellence, PBAC Pharmaceutical Benefit and Advisory Committee, QALY quality-adjusted life-year, RCT randomised controlled trial, SE surrogate endpoint, TA technology appraisal

^aGuide to the methods of technology appraisal

^bMTEP methods guide

surrogate validation studies will never be satisfied for many indications requiring medical device-based procedures. When confronted with this challenge, there is a temptation to extrapolate validated surrogate endpoints from RCTs of medicines (e.g. the use of systolic blood pressure from RCTs of antihypertensive medicines) to medical-device-based therapies (e.g. renal denervation therapy). However, we caution against this approach, given that different modes of action and classes of therapies are known to affect the surrogate-to-final-outcome relationship.

Our study provides a comprehensive contemporary review of methods guidance across international HTA agencies on the use of surrogate endpoints. We explored a larger sample of agencies and documents than did the previous survey [17]. However, available resources (particularly time and linguistic access) limited the inclusion of non-European agencies to those of Australia and Canada. Furthermore, this survey only looked at publicly available documents and not at internal documentation that may be circulated within HTA agencies. As described in Sect. 2, methodological advisory documents [27, 30] were also considered, as—in our opinion—they constitute important material to inform and complement methods practice.

5 Conclusion

This updated survey of international HTA agencies demonstrates an increase in the methodological guidance for the use of surrogate endpoints over the last decade, largely based on the adoption of EUnetHTA guidance on surrogates published in 2015. Nevertheless, we found considerable differences in the depth of this guidance, with only a few agencies currently having guidelines that provide detailed methodological advice on the statistical methods and metrics for surrogate validation that are deemed acceptable. Further methodological and policy research in the harmonization of approaches to surrogate outcomes evidence in healthcare decision making is warranted. The recent EU proposal of joint HTA clinical assessment [38] may provide the opportunity for implementation of a harmonised approach to the validation of the handling of surrogate endpoints across Europe. Our study also suggests an almost exclusive consideration of surrogate endpoints from a clinical efficacy/effectiveness perspective. Opportunities therefore remain to further clarify the effective and consistent use of surrogate endpoints in other HTA domains, especially safety and cost effectiveness.

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Data Availability The data that support the findings of this study are available within the article or its supplementary materials.

Compliance with Ethical Standards

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